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A METHOD OF EXCLUDING BILE FROM THE INTESTINE WITHOUT EXTERNAL FISTULA

By RICHARD M. PEARCE and A. B. EISENBREY

[From the John Herr Musser Department of Research Medicine, University of Pennsylvania, Philadelphia]

THE usual method of diverting bile from the intestinal canal is through the establishment of an external fistula. This method has several disadvantages, of which the most important is the difficulty of carrying an animal for periods of more than two or three weeks without the development of disturbing complications, as infection of the liver, or peritoneum, or, as not infrequently happens, general jaundice due to incomplete drainage. Also, the external fistula presents many difficulties in the collection of the bile and as the flow usually diminishes greatly after the first few days the amount of bile secreted may be so reduced as to prevent satisfactory chemical analysis.

During the past two years it was found necessary in connection with studies on the relation of the spleen to blood destruction to develop some method by which bile might be collected quantitatively over long periods of time. As the external fistula proved unsatisfactory, an operative procedure was elaborated by which, after removal of one kidney, the common duct was sutured to the ureter and the bile thus carried to the urinary bladder and passed with the urine. In some instances the desired result was obtained and the bile was eliminated without

apparent resorption; in other instances local obstruction at the point of anastomosis was responsible for a damming back of bile into the liver with consequent absorption and general jaundice; in a few such cases some bile was, however, passed more or less intermittently in the urine. With the latter outcome the experiment approached the conditions characteristic of jaundice in man — partial or intermittent obstruction with continual absorption and therefore a chronic jaundice — lasting sometimes for months. On the other hand, when the common-duct ureter anastomosis remained patent, the animal survived for months with complete exclusion of bile from the intestine, without absorption jaundice, and with, presumably, the recovery of all bile in the urine.

Although this experimental procedure failed to aid in the elucidation of the problem which we had in mind, largely because of the impossibility of separating, chemically, substances common to both urine and bile, it seems advisable, on account of the availability of the method for various physiologic and pharmacologic studies, to describe the operative procedure and our general results.

The general technic of the operation is as follows: The animal is placed for a day or two on a restricted soft-diet of bread and water, or bread and milk, and twelve hours before operation is given a large dose of castor oil. Under ether anesthesia, by the insufflation method, and with the most careful asepsis, an incision is made through the right rectus muscle from the costal margin to a point midway between the umbilicus and the pubis. The right kidney is isolated after ligation of its artery and vein and the upper end of the ureter with a small portion of the pelvis of the kidney is dissected free and severed with fine scissors, care being exercised to disturb the blood supply as little as possible. The kidney is then removed. The common duct is dissected free well into the duodenal wall and severed close to the papilla after being closed by a Crile carotid clamp. The upper end of the ureter, where it broadens out into the pelvis of the kidney, is then united to the distal end of the common duct by the Carrel vessel-suture method, and a fold of omentum is wrapped about the point of union and sutured in place. In dissecting both ureter and duct as much adventitious

tissue as possible is preserved and is included in the sutures. This is especially important in the case of the ureter which has a very delicate structure from which the sutures easily tear out. The incision is closed by layers, the final skin suturing being subcutaneous with iodine catgut. The wound is painted with iodine and no further dressing applied. The greatest difficulty in the operation is the approximation and accurate coaptation of ureter and duct. With a kidney lying low in the flank and a correspondingly short ureter, considerable tension must be exerted to bring ureter and duct ends together and under such circumstances satisfactory suturing is difficult. In the absence of this anatomical difficulty, a successful result is obtained in a considerable number of experiments.

Of twelve dogs operated upon in this way the result in five, representing the early period of experimentation, was unsuccessful, on account of faulty technic; two succumbed to accidents not ascribable to the operation; and five survived for periods varying from 49 to 248 days. The animals of the first group died or were chloroformed on the 2d (two) 3d, 5th, and 10th days, respectively. In all of these, the duct-ureter tube was patent and bile appeared in the urine, but faulty suturing or too great tension led to leakage with or without local necrosis and peritoneal lesion due to the action of the escaping bile or to infection. Vomiting was always a concomitant of such accidents and upon its development the animal was usually chloroformed. Post mortem examination always revealed a bile stained, sometimes bloody, fluid in the peritoneal cavity. The serosa of intestines and stomach were deeply injected and sometimes hemorrhagic. In no instance was bile found in the intestine and the gall bladder was usually somewhat distended.

Of the second group, in which early death was due to causes other than the operation, one animal succumbed to a severe broncho-pneumonia on the 14th day and the other died on the 19th day while being etherized for the purpose of dressing the wound. In the first, the anastomosis had healed without leaking, but the lumen was constricted at the point of suturing and although some bile passed to the urinary bladder, the obstruction had been sufficient to cause distention of the gall bladder

and absorption of bile with consequent jaundice. In the second animal the anastomosis had healed perfectly, bile passed freely to the urinary bladder, the feces were greyish white in color, the intestinal canal was free of bile and no evidence of obstructive jaundice was present.

The results in the five animals which survived the operation for considerable periods of time are as follows:

Dog **1319**. The operation was on January 28, and the animal died on March 18, the period of survival being 49 days. Bile was passed constantly with urine and there was no evidence at any time of obstructive jaundice. The animal had a good appetite and ate well, but shortly before death showed progressive emaciation and general weakness. The post mortem examination showed perfect healing of anastomosis and no evidence of jaundice. All organs appeared normal except the kidney, which was the seat of a mild pyelonephritis, and the urinary bladder which contained an alkaline urine and exhibited a thickened congested mucosa (Chronic Cystitis). No sufficient cause for death was evident.

Dog **122**. The operation was on October 2, and the animal died on December 29, the period of survival being 88 days. At first bile passed freely into the bladder in large amounts, but gradually diminished after the second week and at about the same time the sclerae and gums showed the yellowish staining of jaundice; for several weeks before death jaundice was well marked. The animal did not eat well and though various changes in diet were made, the weight dropped from 6650 before operation to 4460 on November 9; later daily exercise and an improvement in appetite led to an increase in weight on December 13 to 5060 gm. Despite this improvement, on December 23, the animal developed a typical tetany most noticeable in the fore legs and with typical fibrillation of the tongue. This improved somewhat on the 26th but before a study of calcium metabolism could be completed the animal died on the 29th.

Post mortem examination revealed complete obliteration of the common-duct-ureter tube at the point of anastomosis, thus explaining the severe jaundice, which was evident in all tissues of the body. The gall bladder and common, cystic and intrahepatic ducts, were greatly distended and filled with a thick blackish bile of mush-like consistence. The liver was bile stained, congested and more or less indurated. The left kidney was bile

stained and hemorrhagic and the seat of a well-marked pyelonephritis; in the pelvis was a whitish yellow concretion 1 cm. in length and half a centimetre in thickness. The urinary bladder presented the lesions of chronic cystitis. The mucosa of colon and rectum was hemorrhagic; otherwise the alimentary canal showed no changes. The feces were greyish white in color, fatty, and had a disagreeable odor.

Dog **1120**. The operation was on December 8, 1911; and the animal was killed by chloroform on May 8, 1912, on account of the development of mange and swelling of the joints. The post-operative period was, 151 days. Bile was passed constantly with the urine, the stools were soft and light colored; the appetite was good, but the weight fell during the period of observation from 9760 to 8210 gm. No evidence of obstructive jaundice was seen. Upon post mortem examination hemorrhages were found about the joints, in the subcutaneous tissues of the neck, beneath the mucosa of the tongue, in the anterior mediastinum and about the thoracic aorta. No icteric pigmentation of skin, mucus membrane or sclerae could be discerned. The left kidney was normal in appearance and did not seem to be enlarged; its ureter was normal. The right kidney was absent and the site of its vessels was smoothly healed over. The right ureter was twice the size of the left, somewhat thickened and yellowish in color. Its lumen was free and the peritoneal covering smooth.

The gall-bladder was small and appeared to be somewhat atrophied. The hepatic ducts were very slightly thickened and enlarged and rather whitish in color. The common duct blended with the upper end of the right ureter and the line of union was difficult to make out. No communication between bile passages and intestines could be found.

The urinary bladder appeared normal except for a slightly yellow staining of the mucosa and somewhat thickened walls. The urine within it was rich in bile pigments.

The colon contained considerable soft greasy fecal material of rancid odor and greyish white color. The material in the small intestine showed no evidence of the presence of bile.

Dog **123**. The operation was on October 31, 1912; and the animal died on June 23, 1913, the period of survival being 235 days or about 8 months. Bile passed readily into the bladder, but on December 16, the sclera and the mucous membranes of the mouth showed slight evidence of jaundice which continued without

becoming severe until death. The feces remained free of bile pigment. Despite exercise, frequent changes in diet, and every possible effort to maintain the general condition, progressive loss in weight occurred. This is shown by the following weights: October 29, 10,680 gm.; November 4, 9575 gm.; November 13, 8605; December 13, 7810; December 30, 7000; January 20, 6515; after January the weight remained practically constant, the lowest weight being 5960 gm. on June 2.

The autopsy showed evidence of jaundice and in the tip of the Spigelian lobe of the liver, small yellowish white masses occupying an area of about 3 cm. in diameter. The right ureter could be traced up from the bladder as a thin, normal looking structure ending in a mass of adhesions behind the pancreas. A probe could be passed readily from the lower end of the ureter into the hepatic duct, there being no appreciable constriction at the point of anastomosis. The probe, however, could not be passed into the gall bladder but on pressure bile could be forced from the gall bladder into the duct. The obstruction to the flow of bile was apparently due to the effect of adhesions. The left kidney and ureter appeared normal. The urinary bladder was somewhat bile stained and the seat of a trabecular hypertrophy with injection of the trigone and chronic cystitis. The right lung showed a few small patches of broncho-pneumonia.

Dog **1318**. The operation was on January 28, 1913, and the animal was killed by chloroform, on account of the development of mange, on October 3. The period of survival was 248 days. Bile passed freely at all times into the urinary bladder and at no time did evidence of jaundice appear. The feces were greyish white in color, of foul odor and at all times free of bile pigment. Unfortunately the record of early weights was lost, but on May 10, the weight was 5970 gm., on June 19, 6650 gm., with an increase on July 22 to 6780 gm.; at the end of the experiment the weight was 6690 gm. The autopsy showed the common duct-ureter tube to be patent from gall-bladder to urinary bladder, with slight thickening of its wall at point of anastomosis. The gall bladder was slightly distended but otherwise no evidence of interference with the flow of bile was present. The remaining kidney and the bladder showed no lesions.

This summary shows a perfect operative result in five dogs, surviving for 49, 88, 151, 235, and 248 days respectively, and

without, in three, the occurrence of obstructive jaundice. In a fourth animal, complete occlusion occurred finally at the point of anastomosis and after a long period of obstructive jaundice death occurred on the 88th day; in the fifth dog which survived until the 235th day, the duct-ureter anastomosis was patent, but adhesions interfered with the flow of bile and a slight persistent jaundice occurred. These results demonstrate the possibility of utilizing the procedure for the study of the effects of absence of bile from the intestine during long periods of time without, as was possible in three of these animals, the presence of obstructive jaundice. On the other hand, the procedure when followed by obstructive jaundice, as in two of these dogs, offers a more satisfactory experimental condition for the study of the effect of chronic jaundice than does the well-known ligation experiment.

There is, however, a modification of the technic which may be used when it is desired to secure the urine free from the admixture with bile. This consists in performing an operation secondary to the common-duct-ureter anastomosis, by which the ureter is severed at its entrance into the urinary bladder, and is implanted by Coffey's method into the lower colon. This, however, is usually followed, as in one of our animals which survived the procedure for 77 days, by a well-marked jaundice, and is frequently complicated by ascending infection from the colon. This experimental procedure, the two steps of which may be completed at the one operation, provides a method of studying the influence of the absence of bile upon the processes of digestion and absorption in the upper intestine that is of especial value in that it leaves the urine free of admixture with bile.

The question of infection is not limited, however, to the colon anastomosis. In the simple common-duct-ureter anastomosis, the urine early becomes alkaline, pus cells appear in it, and as shown in the notes, chronic cystitis, at times with pyelonephritis, and occasionally pelvic calculus, occurs in the long time experiments. That this complication might seriously interfere with the successful completion of experiments in which exact chemical investigation is essential, is evident.

Lesions observed in two of the animals described above, deserve a word of special comment. In one (Dog 1120) a widespread and severe hemorrhagic condition was present. If this had occurred in connection with jaundice, the common association of hemorrhage and jaundice might be invoked as a possible explanation, but in the absence of jaundice we have no suggestion to offer. In a second animal (Dog 122) with well-marked jaundice, typical tetany developed a short time before death. The occurrence of this symptom may have been purely accidental and this possibility is supported by the fact that when the parathyroids were examined histologically they were found to contain a marked increase of connective tissue. As, however, the observations of King[1] and his associates on the increased elimination of calcium in obstructive jaundice suggested a possible disturbance of calcium metabolism, a study of the calcium balance was made. This was not completed with the dog in question on account of an early fatal termination, but with one other animal (Dog 123), the following results[2] were obtained:

TABLE I. Calcium Elimination[2] — Dog 123. Operation, October 31, 1912; Death, June 23, 1913.

Period	Dates	Calcium output	Excess over intake
4 days	February 13–17	0.323 g.	0.255 g.
4 days	February 17–21	0.327 g.	0.259 g.
5 days	May 12–16	0.385 g.	0.289 g.

In this study the animal was placed on a constant diet of beef heart, the calcium content of which was determined. The calcium of urine and feces after incineration was determined, in each separately, by McCrudden's method with titration by potassium permanganate.

[1] King, J. H., Bigelow, J. E., and Pearce, L.: Journal of experimental medicine, 1911, xiv, p. 159.

[2] For these chemical analyses and for assistance in several operations we are indebted to Dr. M. M. Peet.

The figures presented show the increased elimination of calcium as described by King, Bigelow and Pearce. The data, however, are not sufficient, even if the relation of calcium to tetany were definitely established, to allow conclusions. It would appear, however, that the occurrence of tetany, as well as the hemorrhagic condition in dog 1120 were purely accidental. This is supported by the absence of such conditions in dog 1318 which survived for 8 months.

Throughout this investigation histological examinations have been made for the purpose of determining the character of the changes in the duct-ureter anastomosis and the possibility of microscopic lesions in the various organs and tissues of the bodies. Nothing of importance has been found. In animals dying a few days after operation the point of anastomosis has shown the usual picture of necrosis and infection; in those dying after long periods, the duct-ureter tube has shown epithelial atrophy, fibrotic thickening and lymphoid cell infiltration with sometimes a dilatation and sometimes a narrowing of the lumen. In one instance (Dog 122) complete obliteration was present. The urinary bladder has sometimes shown the histological picture of chronic cystitis and the remaining kidney that of pyelonephritis. Aside from the liver which has occasionally shown evidence of bile stasis or of recent or old infection, the changes in the other organs have not been important.

Summary

A method of value in the experimental study of the physiology of the bile consists in diverting the bile from the intestine to the urinary bladder by anastomosing the common bile duct and the right ureter after removal of the corresponding kidney. This procedure leaves the intestine completely free of bile and allows the collection of total secretion of bile mixed with urine. The procedure is not free from undesirable complications, as infection of urinary bladder and kidney may occur, but as animals survive with good flow of bile for periods varying from seven weeks to eight months it is more satisfactory than the external fistula. The mixture of urine and bile renders diffi-

cult however quantitative chemical examinations. If it is desirable to study the urine unmixed with bile the lower end of the ureter may be implanted in the colon, thus leaving the upper intestine free of the action of bile, and still avoiding the troubles of the external fistula. The colon implantation tends, however, to greater ease of infection. One difficulty, in either procedure lies in the fact that changes at the site of the common-duct-ureter or ureter-colon anastomosis may occasionally prevent free flow of bile and lead to obstructive jaundice. This occurred in two of our five animals. When, however, this obstruction is not so complete as to lead to early death it offers a form of chronic obstructive jaundice which is much more satisfactory for experimental study and resembles more closely that occurring in man than does that produced by ligation of the common duct.

Although we have been unable — largely because of the difficulty of studying chemically a bile-urine mixture — to solve the problem in connection with which this technical method was developed, we offer the results of our use of it, in the hope that others may find in it a method of approaching some of the problems concerning the bile, in its many relations, and perhaps also an aid in pharmacological studies.

A COMPARISON OF THE AUSCULTATORY BLOOD PRESSURE PHENOMENON IN MAN WITH THE TRACING OF THE ERLANGER SPHYGMOMANOMETER

By ARTHUR W. WEYSSE and BRENTON R. LUTZ

[*From the Physiological Laboratory of Boston University*]

Introduction

THE sphygmomanometer has come into such general use in practical medicine as well as in the laboratory within recent years that it becomes imperative to establish such criteria for the determination of the blood pressure by the various methods employed, that the records of different observers may be comparable. The auscultatory method seems to be particularly reliable, but there has been no conclusive demonstration of the relation of the auscultatory phenomenon in man to the record of an accurate graphic instrument. In this paper we present the results of a comparison of the auscultatory method with the tracings from the Erlanger sphygmomanometer.

The Criteria for Maximum and Minimum Blood Pressure

The criteria used for the determination of maximum blood pressure with the Erlanger sphygmomanometer are: (1) a marked increase in amplitude of the pulsations traced on the cylinder; (2) a change in the direction of the trough line; (3) a change in form of the pulse wave. (Erlanger, 1904 and 1908.)

The minimum blood pressure is determined by the maximum oscillations obtained with the Erlanger sphygmomanometer. Howell and Brush (1901) showed conclusively by animal experimentation that maximum oscillations occur when the artery is subjected to an external pressure equal to the minimum blood

pressure, and Erlanger (1904) has shown with an artificial circulation, in which was inserted a piece of artery, that maximum oscillations are obtained with his instrument at minimum pressure. Hence he considers the marked decrease in amplitude of the oscillations as an index for minimum blood pressure.

In the auscultatory method described by Korotkoff in 1905 we now distinguish the five phases first recognized by Ettinger (1907), as follows; 1st, first sounds, clear; 2d, murmurs; 3d, clear sounds; 4th, dull sounds; 5th, cessation of the sounds.

All observers agree that the beginning of the 1st phase is coincident with maximum pressure. But the criterion for minimum pressure is in dispute; such observers as Fischer (1908), Lang and Manswetowa (1908), Van Westenrijk (1908), and Warfield (1912) consider the beginning of the 4th phase as the auscultatory index for minimum pressure; while Ettinger (1907), Gittings (1910), and Goodman and A. A. Howell (1910) consider the 5th phase as the correct index.

A Brief Review of the Literature

Korotkoff (1905), as reported by Schrumpf and Zabel (1909), heard the first sound before the pulse could be palpated at the wrist, the difference being represented by from 10 to 12 mm. of Hg. He measured the minimum pressure after the "endtöne," i.e. at what is now called the 5th phase.

Ettinger (1907) compared the auscultatory with the palpatory and graphic methods. He considered the first sound as an index to maximum pressure, and the cessation of all sounds, i.e. the 5th phase, as an index to minimum pressure. Out of 232 determinations, he found that 207 times the auscultatory maximum was higher than the graphic maximum (Janeway-Massing) or the palpatory maximum (Strassburger). Out of 227 determinations of the minimum pressure he found that 130 times the auscultatory minimum was lower than the palpatory or the graphic, 18 times it agreed with them, 71 times it was higher than either, and 8 times between the two. In general he found the maximum higher and the minimum lower with the auscultatory method.

Lang and Manswetowa (1908), comparing the auscultatory method with the oscillatory method of v. Recklinghausen, found that when the first sound was heard the amplitude of the oscillations showed a marked increase. During the 3rd phase the intensity of the sounds and the amplitude of the oscillations were proportional. At the moment the amplitude began to decrease the sounds became dull, indicating the onset of the 4th phase. This first decrease in the height of the oscillations and the beginning of the 4th phase, these authors believe indicate minimum blood pressure. Experiments with two large dogs led them to the same conclusion.

Van Westernrijk (1908), comparing simultaneously the auscultatory method with Uskoff's graphic method, found no constant relation between the 4th phase and the maximum oscillations obtained with the Uskoff sphygmotonograph. (Erlanger [1908] shows that the Uskoff sphygmotonograph has a physical defect.) He observed, however, a definite relation between the auscultatory phenomenon and the oscillations of Pal's sphygmoscope. The marked increase in amplitude of the oscillations was coincident with the first sound, and the sudden diminution in amplitude occurred at the beginning of what is now called the 4th phase.

Fischer (1908), comparing the auscultatory method with the oscillatory method of v. Recklinghausen, found in 150 cases, normal and abnormal, the maximum determined by both methods agreed 58 times. In 92 cases the oscillatory maximum was higher than the auscultatory maximum. In these same 150 cases he determined the minimum pressure by both methods and found it agreed in 47 cases; in 97 cases the oscillatory minimum was lower than the auscultatory; in 6 cases it was higher. He concluded the 4th phase to be the most accurate index, and found in cases of long 4th phase a low minimum pressure, and in cases of short 4th phase a high minimum.

Gittings (1910), and Goodman and A. A. Howell (1910) consider the 5th phase as an index to minimum blood pressure. The latter even go so far as to say that "it is generally agreed that the disappearance of all sound is coincident with minimal or diastolic pressure." Gittings found in 41 cases out of 48 that

the minimum pressure determined at the 5th phase averaged 15.5 mm. of Hg lower than when determined by the visual method.

When our investigation was nearly completed the preliminary report of Warfield (Oct. 1912) appeared, in which he questions the accuracy of the 5th phase as an index to minimum pressure. He used one of the tambours of the Hirschfelder attachment to the Erlanger instrument, fitted with a pipette bulb and a lever, to record the auscultatory phenomenon simultaneously with the blood pressure tracing. He publishes five records (in four of which the pressure recorded is above 150 mm. of Hg) to show the relation of the tracing to the auscultatory phenomenon. The 1st phase coincides with the graphic maximum, but the relation of the 4th phase to the graphic minimum is not clearly shown by his records, yet it is evident that the 5th phase does not correspond to maximum oscillations. He does not state how many cases he has examined. He concludes that the diastolic pressure is not usually at the point of disappearance of all sound, the 5th phase. In a still more recent article (1913) he publishes tracings which demonstrate that the 4th phase coincides with the minimum pressure as recorded by the Erlanger sphygmomanometer.

In another publication (Sept., 1912) Warfield describes his experiments on three dogs, using a method by which he can measure the diastolic pressure by the auscultatory phenomenon, taking as a point of diastolic measurement the sudden dulling of the sound. He says that the sounds heard in the femoral artery of a dog are not like those heard in the brachial artery of man, but correspond in a general way. We may infer, then, that he reads the minimum pressure at the beginning of the 4th phase. By means of a maximum and minimum manometer, and an improvised plethysmograph he shows that this sudden change of sound in the artery of a dog takes place at minimum pressure.

Brief reference may be made to the paper of Taussig and Cook (1913) in which they state that minimum pressure should be read at the 4th phase.

Subjects, Apparatus, and Method

In this investigation sixty-one healthy students were used as subjects. Four of them were women.

An Erlanger apparatus was used, to which was attached the tambour and writing lever of a pneumograph, and two signal-magnet levers, one to mark the auscultatory phases, and the other to record the height of the mercury column. (Fig. 1.) A Bowles sphygmometroscope was used for auscultation.

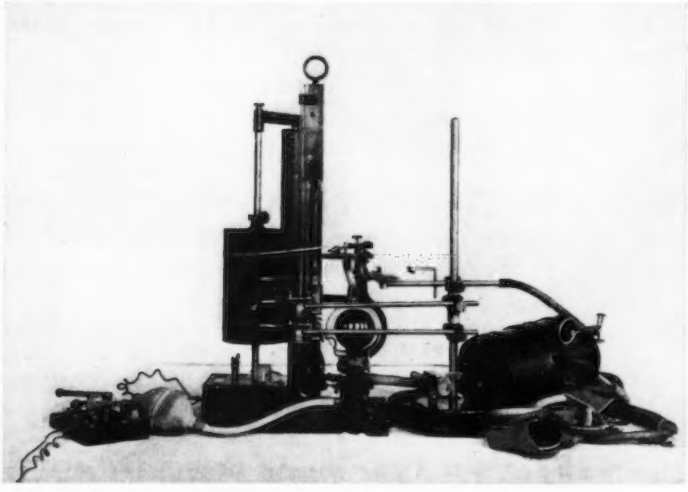


Figure 1. Arrangement of the apparatus.

All the determinations were made on the right arm of the subject, who was seated, so that the cuff of the sphygmomanometer was approximately on the level of the heart. After the levers were put in vertical alignment the pressure was raised to well above maximum and then lowered by the continuous escapement method. The observer recorded the onset of each phase, in some cases waiting one or two pulse beats to make sure of the change, and looked only at the manometer scale in order to record the height of the mercury every 5 mm., and to

record the auscultatory phases without being influenced by any changes in the graphic record. In this way a comparative record was made, which showed the relation of the auscultatory phases to the changes in the blood pressure tracing. The levers occupied the same relative positions in all the tracings as shown on the accompanying figures. The first or uppermost recorded the blood pressure, the second respiration, the third the auscultatory phases, the fourth the height of the mercury column.

Results

The chief object was to determine the auscultatory index of minimum pressure, and incidentally to check the accuracy of the criteria for the determination of maximum pressure with the Erlanger instrument, since in former work we experienced some difficulty in many cases in obtaining satisfactory readings from the tracings.

Out of 210 comparative determinations on 61 different individuals, the graphic maximum could be read 134 times, while the auscultatory maximum was obtained 206 times; or, 76 times the graphic could not be read, and 4 times the auscultatory maximum was not recorded. These results may be tabulated as follows:

Number of subjects	61
" " graphic records	210
" " " " in which maximum pressure was obvious	134 or 63.3%
" " " " " " " " could not be read	76
" " cases in which maximum pressure was obvious by auscultation	206 or 98.9%

Of the 134 graphic records mentioned 128 showed the auscultatory maximum equal to or only from 1 to 5 m. of Hg below the graphic maximum; 3 times it was from 1 to 5 mm. above, and 3 times from 5 to 10 mm. below. In these 134 cases, then, the graphic maximum agreed with the 1st phase in 95.5% of the determinations.

Out of the 210 cases the graphic minimum could be read 142 times, while the auscultatory 4th phase was recorded 183

times; or, 68 times the graphic minimum could not be read; 27 times the 4th phase was not recorded because the sounds became dull so gradually that the exact point could not be determined. These results may be tabulated as follows:

Number of subjects	61
" " graphic records	210
" " " " in which minimum pressure was obvious	142 or 67.6%
" " " " " " " " could not be read	68
" " cases in which the 4th phase was obvious	183 or 87.1%

Of the 142 cases mentioned, 108 showed the onset of the 4th phase equal to or only from 1 to 5 mm. below the marked decrease in amplitude of the oscillations; 28 times it was from 1 to 5 mm. above, and 5 times from 5 to 10 mm. below. In these 142 cases, then, the 4th phase agreed with the graphic minimum in 77.4% of the determinations.

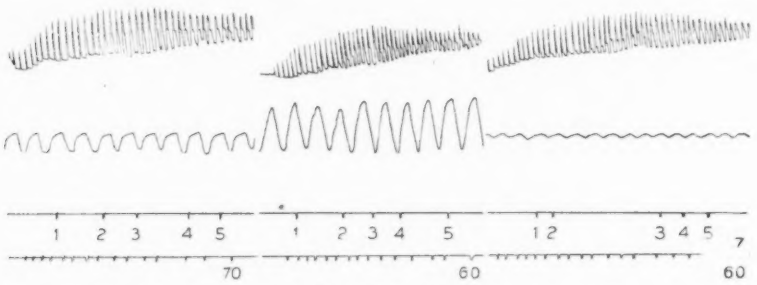
In all of the 210 records the 5th phase occurred from 10 to 25 mm. of Hg below maximum oscillations, and in no way coincident with the diminution of amplitude. (Fig. 5.)

In 36.8% of the determinations no readings of the maximum pressure could be obtained with the Erlanger instrument; and in 32.3% no readings of minimum pressure could be obtained. The reason for this percentage of unsatisfactory determinations is not to be found in any peculiarities of the subjects but in factors active when the records were taken, since out of the three or four determinations made on each person two or three satisfactory readings were nearly always obtained.

Among the factors that might affect the record of the sphygmomanometer are movements of the arm, contractions of muscles under the cuff, changes in the vascularity of the arm, and the changes in blood pressure due to respiration. Movements of the arm or the contraction of muscles under the cuff occurring at the time the external pressure is about to equal the maximum blood pressure would undoubtedly alter the usual changes in the sphygmomanometric record by changing the pressure within the cuff. Changes in vascularity affecting the volume of the

arm would tend to affect the record in a similar manner, and sudden vasomotor changes or rhythmical waves of blood pressure would likewise have an effect.

Respiration has sometimes a marked effect upon the determinations. Erlanger and Festerling (1912) have shown that arterial blood pressure rises during expiration and falls during inspiration. With the rise in blood pressure there is an increase in the amplitude of the oscillations recorded, — with the fall a decrease occurs. Venous pressure as well falls during inspiration, and this coupled with the fall of arterial pressure would reduce the volume of the arm, causing a lowering of the pressure in the cuff, a condition that would cause an increase in ampli-



FIGURES 2 and 3. In these and all the following records the upper curve represents the blood pressure, the next curve the pneumograph tracing, the third line indicates the auscultatory phases, the lowermost line the fall of the Hg column at intervals of 5 mm. These records show clearly the relation between the auscultatory phases and the blood-pressure tracing, and also that maximum pressure occurs on expiration and minimum pressure on inspiration. Figure 2, maximum pressure 123 mm. of Hg, minimum 82 mm. Figure 3, maximum 125 mm., minimum 80 mm.

FIGURE 4. Similar to records 2 and 3, but illustrating a long 2d phase. Maximum pressure 125 mm., minimum 73 mm.

tude of the oscillations. However, this is more than offset by the greater direct effect of the inspiratory fall of arterial pressure which is manifest on the record as a decrease in amplitude. It is theoretically probable that the expiratory rise of arterial pressure, when it occurs at the time that the pressure in the cuff is about to equal the maximum blood pressure, would tend to accentuate the criteria for determining the latter; under similar conditions the inspiratory fall would tend to obscure

them. The graphic minimum should be affected as well, and a decrease in the amplitude of the oscillations should occur with inspiration.

Our records would seem to indicate that the graphic maximum occurs during expiration, i.e. on the upstroke of the pneumograph lever, and the graphic minimum during inspiration, but we are not prepared to say that this is true in all cases. Compare Figs. 2, 3 and 4. The effect of the respiratory changes on the blood pressure is clearly marked in Fig. 7, where the sounds alternate between the 3rd and 4th auscultatory phases synchronously with the respiratory movements, and also in Fig. 6, where the 1st phase disappeared as a result of inspiration

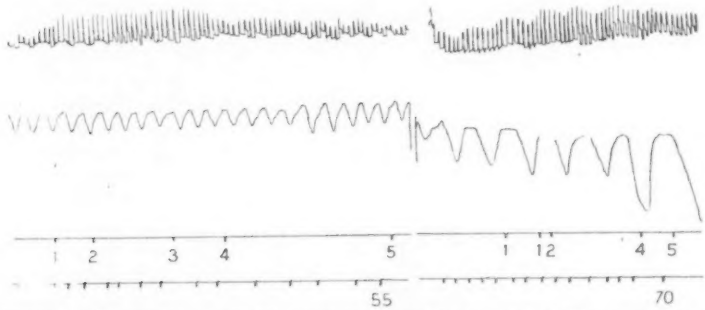


FIGURE 5. Illustrating a long 4th phase corresponding to a fall of 25 mm. of Hg, and showing the error that would result from reading the minimum pressure at the 5th phase instead of at the beginning of the 4th. Maximum pressure 120 mm. of Hg, minimum 82 mm.

FIGURE 6. This record illustrates the disappearance of the first sound on inspiration and its reappearance on expiration.

and then reappeared. The cases in which this phenomenon was observed showed a slightly greater cardiac arhythmia than is present in most normal individuals, and in one case at least the degree of this arhythmia varied on different occasions as in Figs. 7 and 8 which were taken on the same individual at an interval of about four weeks. We are inclined to attribute this slight increase in arhythmia to an increased susceptibility of the heart to respiration.

Goodman and A. A. Howell (1911) note changes occurring in the phases themselves, which they call tonal arhythmia or an

alternation of the intensity of the individual sounds, and they regard this arhythmia as evidence of variation of the contractions of the heart. They observe also poor differentiation of the phases, e.g. cases in which murmurs may alternate with tone beats, or dull tones with sharp tones and they believe this to be an evidence of cardiac weakness. These phenomena are identi-

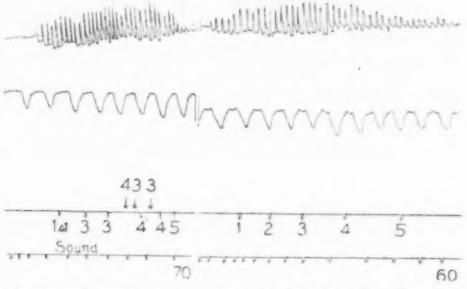


FIGURE 7. In this record no 2d phase was distinguished. The 3d phase diminished in intensity shortly after its appearance and then recovered to be followed by alternating 4th and 3d phases synchronously with inspiration and expiration.

FIGURE 8. Record taken from the same individual as Fig. 7, but about four weeks earlier and showing the absence of the alternating phases there indicated.

cal with those which we have just pointed out in our records, but these authors have not called attention to the influence of respiration on the heart beat, a factor that seems to us to be indicated by our tracings.

Goodman and A. A. Howell (1911) have studied the relative length of the various auscultatory phases, and our records confirm, in general, their results as is evident from the auscultatory tracings in the accompanying figures. The largest oscillations appear with the 3rd phase, and our tracings confirm the conclusions of Lang and Manswetowa (1908) when they say that the height of the oscillations and the intensity of the sounds are proportional.

CONCLUSIONS

1. Maximum pressure as determined with the Erlanger sphygmomanometer on normal individuals is coincident with the onset of the 1st phase of the auscultatory phenomenon.

2. Minimum pressure as determined with Erlanger's instru-

ment on normal individuals is coincident with the onset of the 4th phase.

3. Since the onset of the 4th phase is coincident with the marked decrease in amplitude of the oscillations recorded by the Erlanger sphygmomanometer, it should be considered as the index of minimum blood pressure.

4. Since the 5th phase occurs later than the last maximum oscillations, — in some of our cases (e.g. Fig. 5) as much as 25 mm. of Hg, — it should not be taken as the index of minimum pressure.

5. Maximum pressure occurs commonly, if not always, during expiration, and minimum pressure commonly, if not always, during inspiration.

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STUDIES IN FATIGUE

II. The Threshold Stimulus as Affected by Fatigue and Subsequent Rest

By CHARLES M. GRUBER

[From the Laboratory of Physiology in the Harvard Medical School]

As a muscle approaches fatigue its contractions decrease in height. Higher contractions will again be elicited if the stimulus is increased. Although these phenomena are well-known, no adequate analysis of their causes has yet been advanced. A number of factors are probably operative in decreasing the height of contraction: (1) the using up of available energy-producing material; (2) the accumulation of metabolites in the fatigued muscle; (3) polarization of the nerve at the point of repeated stimulation and (4) a decrease in irritability, i.e., an increase in the threshold stimulus. It may be that there are interactions between these factors within the muscle, e.g., the second may cause the fourth.

The last of these factors — the effect of fatigue on the threshold stimulus — has been the subject of this investigation. The effect of subsequent rest on the fatigue threshold has also been studied.

The Method

In earlier experiments the animals (cats) were anaesthetized with urethane (2 gm. per kilo body weight by stomach), but later Sherrington's method of decerebration was employed. First the cats were anaesthetized with ether and the carotid arteries ligated. It was deemed advisable to isolate and cut the sciatic next, before completion of decerebration, since the cutting of a large nerve trunk may increase blood pressure, and thus cause hemorrhage from the vessels opened in decerebration. From this

point the method was similar to that described by Forbes.[1] The vertebral arteries were clamped off by applying pressure with the forefinger and thumb, one on either side of the neck, just below the transverse processes of the axis during the time that the cerebral hemispheres were being removed from the cranium, and until the blood in the wound was sufficiently coagulated to prevent hemorrhage. In the few cases in which the lack of blood to the respiratory centre stopped normal respiration, artificial respiration was employed until the release of pressure on the vertebral arteries allowed normal respiration to return.[2]

The nerve-muscle preparation. — By enlarging the slit in the skin made for cutting the sciatic, the *peroneus communis* nerve was bared and along its entire length separated from the *tibialis* nerve.[3] Its distal end was then fastened in a Sherrington shielded electrode, which was held in place by fastening around it with spring clips the two flaps of skin.[4] This electrode was used in fatiguing the muscle. A second Sherrington electrode having a slit on one side, which permitted quick adjustment on the nerve, was placed between the first electrode and the muscle each time that a series of readings of the threshold and resistance were taken, and removed after each series in order to avoid possible short circuiting (from moisture) between the platinum points. Since this electrode was used only in determining the threshold, polarization of the nerve was also avoided. Although resistances were taken with each series of readings care was used to place this second electrode in a similar position each time. In the later experiments a double Sherrington shielded electrode was substituted for the two single electrodes. In this case the platinum points further from the muscle were used for stimulation during fatigue, and the others — nearer the muscle — for measuring the threshold. Here, as before, the points used in determining the threshold stimulus were removed and the

[1] Forbes: Quarterly journal of experimental physiology, 1912, v. p. 166.

[2] I wish to thank Dr. Alexander Forbes for demonstrating to me the method here cited.

[3] The nomenclature here employed is that of Reighard and Jennings: The anatomy of the cat, New York, 1901.

[4] Sherrington: Journal of physiology, 1909, xxxviii, p. 382.

moisture wiped from them and the nerve before each threshold determination.

The skin and underlying tissues were cut away from the *tibialis anticus* muscle in two places about 5 cm. apart. Through these openings the threshold stimulus for the muscle was determined by means of platinum needle electrodes thrust into the muscle. The electrodes were removed after each series of readings and the muscle kept moist with Ringer's solution. Local polarization was avoided by reinserting the needles into fresh portions of the exposed areas. Since it is possible to insert the needles into a muscle so that they lie next to a nerve strand, in which case the threshold is diminished, several readings were taken in order to obtain a uniform threshold.

Through another small slit in the skin the tendon of the same muscle was exposed, was isolated from its insertion, and fastened to a muscle lever by a strong thread passing about two pulleys arranged so that the muscle pulled in its normal direction. One leather thong about the hock and another around the foot just below the emergence of the tendon bound the leg to the animal holder and made a preparation having its normal blood supply unaltered except by the cutting of the *peroneus communis* nerve.

The muscle lever consisted of a pivoted steel bar, bearing a straw and writing point. The pull of the lever was about 15 gm. The lever and one pulley were supported by an iron tripod; the other pulley was fastened to the stand upon which the tripod stood. The thread from the tendon was attached to the lever directly above the point at which the spring was attached for fatigue. During threshold determination the lever without the spring was used. While fatiguing the muscle, the spring had, in the majority of cases, a tension of 120 gm. the moment the muscle began to contract, but in many cases it had an initial tension from 180 to 250 gm. The initial tension, however, was uniform during each experiment. For each 2 cm. excursion of the writing point on the drum surface the spring increased 60 gm. above the initial tension. Records of the contracting muscles were taken on a slowly moving drum in order to trace the

fatigue, and in no case was the muscle fatigued to a standstill. Weights — 120 and 200 gm. — were lifted in a few experiments; in all instances the muscle was after-loaded.

A few experiments were performed on animals in which the left *peroneus communis* nerve had been cut aseptically seven to fourteen days before the experiments. In these cases the *tibialis anticus* muscle was fatigued and the threshold determined through platinum needle electrodes thrust into the muscle itself.

The stimulating current for fatigue. — The stimulating current for fatigue was a maximum break induction shock obtained from a modified Martin key.[1] This key, made of vulcanite, is about three times the size of the Martin key and is divided similarly into two chambers — a large one and a small one — each filled with mercury and each bearing one of the poles. The chambers are connected by a small opening 2 mm. in diameter. A vulcanite disc, 8 cm. in diameter, also with an opening, revolves within the large chamber close to the partition and, except at the moment its opening coincides with the opening between the chambers, cuts the connecting column of mercury. In this manner the current is made and broken. In the later experiments a glass plate was fitted in the large chamber between the disc and partition to protect the vulcanite from wearing. A rectangular piece of vulcanite, extending to the bottom of the chamber, is placed close against the disc where it rotates into the mercury. By means of this shield the mercury surface is held stationary, and thus kept from excessive oxidation. A motor running at a uniform rate rotates the disc. The rate of make is varied by a series of pulleys on the motor and also by substituting for the original vulcanite disc other discs with two or more openings.

Because the make shock is subminimal while the break shock is maximal no effort is made to short-circuit it.

The rate of stimulation usually employed for fatigue was 120 stimuli per minute, but 240 was found quite as satisfactory and used in nearly as many cases. This rate was sufficiently slow to produce not vasoconstriction but vasodilation in the

[1] MARTIN: Measurement of induction shocks, New York, 1912, pp. 60–69.

vessels of the stimulated muscle.[1] For fatiguing the normal muscle the secondary of the inductorium was connected with the shielded electrode further from the muscle on the *peroneus communis* nerve; for fatiguing the muscle in which the nerve supply was degenerated, it was connected with the platinum needle electrodes thrust into the muscle itself.

Threshold determinations. — The method used for determining the threshold stimulus was the Martin method in which the strength of stimulus is calculated in β units.[2] When the threshold of the nerve-muscle was taken the apparatus for this determination was connected to the electrode nearer the muscle on the *peroneus communis* nerve, so that the kathode was next to the muscle, and separated from the fatiguing electrode by more than 3 cm. When the threshold of the muscle was taken directly the apparatus was connected to the platinum needle electrodes thrust into the muscle. The position of the secondary coil, in every case, was read by moving it away from the primary coil until the very smallest possible contraction of the muscle was obtained. Four of these readings were made, one with tissue resistance, and others with 10,000, 20,000 and 30,000 ohms resistance in the secondary circuit. Only break shocks were employed, the make shocks being short-circuited by the Martin key. Immediately after the determination of the position of the secondary coil, and before the electrodes were removed or disconnected, three readings of the tissue resistance were made.[3] From these data three values for A, four for β and three values for tissue resistance were calculated as described by Martin, and Grabfield and Martin.[4]

The strength of the primary current for determining the threshold of the nerve-muscle was usually .01 ampere, but in a few cases .05 ampere was used. For normal muscle it was .05 ampere and for denervated muscle 1.0 ampere. The inducto-

[1] BOWDITCH and WARREN: Journal of physiology, 1886, vii, p. 416; BRADFORD: *Ibid.*, 1889, x, p. 390.

[2] MARTIN: *loc. cit.*, pp. 71–93.

[3] MARTIN: *loc. cit.*, p. 26.

[4] MARTIN: *loc. cit.*, pp. 71–93; GRABFIELD and MARTIN: This journal, 1913, xxxi, p. 301.

rium, which was used throughout, had a secondary resistance of 1400 ohms. This was added to the average tissue resistance in making corrections — corrections were made also for core magnetization. In this coil the value of K was 0.22.[1]

The Effect of Fatigue upon the Threshold Stimulus

The threshold for the *peroneus communis* nerve in decerebrate animals varied from 0.319 to 2.96 β units, with an average in sixteen experiments of 1.179. See Table I. This average is the same as that found by E. L. Porter for the radial nerve in the spinal cat.[2] For animals under urethane anaesthesia a higher average β was obtained. In these it varied from .644 to 7.05, or an average in ten experiments of 3.081. See Table II.

The threshold for the *tibialis anticus* muscle varied in the decerebrate animals from 6.75 β units to 33.07, or an average in fifteen experiments of 18.8. Ten experiments were performed under urethane anaesthesia and the threshold varied from 12.53 to 54.9, with an average of 29.849 β units. From these results it seems very evident that the kind of anaesthesia notably affects the threshold.

E. L. Porter will publish in a short time detailed observations showing that the threshold of a nerve-muscle may remain constant for hours. I have obtained the same results in several experiments. If, therefore, after fatigue, a change exists in the threshold this change is necessarily the result of alterations in the nerve-muscle or muscle set up by the fatigue process.

After fatigue, the threshold of the nerve-muscle, in the sixteen decerebrate animals, increased from an average β of 1.179 to 3.34 — an increase of 183 per cent. See Table I. In the ten animals under urethane anaesthesia the threshold after fatigue increased from a normal average β of 3.08 to 9.408 — an increase of 208 per cent. See Table II.

An equal increase in the threshold stimulus was obtained from the normal muscle directly. In decerebrate animals the

[1] See Martin: *loc. cit.*, p. 46; Grabfield and Martin: *loc. cit.*, p. 302.

[2] E. L. Porter: This journal, 1912, xxxi, p. 149.

normal threshold of 18.8 β units was increased by fatigue to 69.54, or an increase of 274 per cent. With urethane anaesthesia the threshold increased from 29.849 to 66.238, or an increase of 122 per cent.

Fig. 1, plotted from the data of one of the many experiments, shows the relative heights of the threshold before and after fatigue. The two readings of the threshold, one from the nerve supplying the muscle and the other from the muscle directly, served as a check on the electrodes. The broken line in the curve represents the threshold (in β units) of the nerve-muscle and the continuous line that of the muscle. The threshold of the nerve-muscle is magnified ten times. In this experiment the threshold of the muscle after fatigue (i.e., at 2) is 167 per cent higher than the normal threshold (1) while that of the nerve-muscle after fatigue is 30.5 per cent higher than its normal.

Evidently a direct relation exists between the duration of the work and the increase in threshold. For instance, the threshold is higher after a muscle is fatigued for two hours than it is at the end of the first hour. The relation between the work done and the threshold is not so clear. In some animals the thresholds are higher after 120 gm. have been lifted 120 times a minute for 30 minutes than in others in which 200 gm. have been lifted 240 times a minute for the same period. The muscle in the latter did almost four times as much work, yet the threshold was lower. This may prove to be a good criterion as to the condition of the animal.

A few experiments were performed on animals in which the nerve supplying the muscle was cut seven to fourteen days previous to the experiment. The average normal threshold for the denervated muscle in 6 animals was 61.28 β units. As in the normal muscle the percentage increase due to fatigue was large.

The Influence of Rest upon the Fatigue Threshold

That rest decreases the fatigue threshold of both nerve-muscle and muscle can be seen from Table III and Fig. 1. The time taken for total recovery, however, is dependent upon the amount of work done, but this change, like that of fatigue, varied widely with different individuals. In some animals the threshold

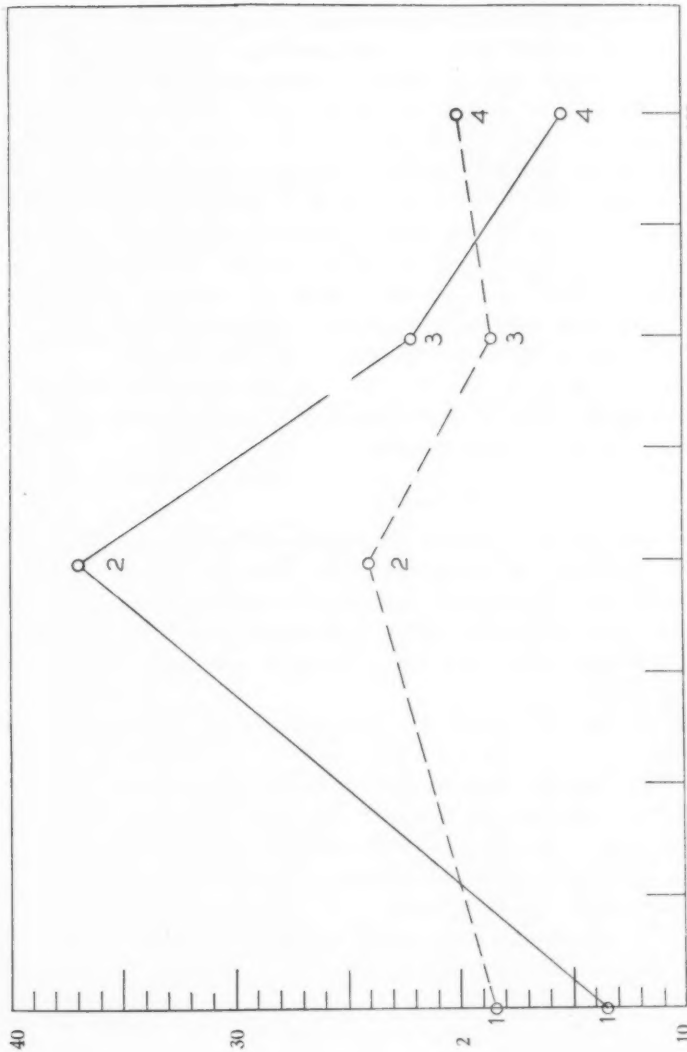

FIGURE 1. A curve plotted from the data of one experiment. The time interval in minutes is represented on the abscissa; the value of the threshold in β units is represented on the ordinate. The continuous line is the curve of the muscle, the broken line that of the nerve-muscle. The β of the nerve-muscle is magnified ten times, that of the muscle is normal.

(1) Normal threshold stimulus.

(2) Threshold after one hour's fatigue lifting 120 gm. 240 times per minute.

(3 and 4) The thresholds after rest.

returned to normal in 15 minutes; in others, in which the same amount of work was done, it was still above normal even after 2 hours' rest. This may be due to the condition of the animals, — in some the metabolites are probably eliminated more rapidly than in others. There were also variations in the rate of restoration of the normal threshold when tested on the nerve and when tested on the muscle in the same animal. In Fig. 1 (at 3) the nerve muscle returned to normal in 30 minutes, whereas the muscle (at 4) after an hour's rest had not returned to normal by a few β units. This, however, is not typical of all nerve-muscles and muscles. The opposite condition — that in which the muscle returned to normal before the nerve-muscle — occurred in as many cases as did the condition just cited.

The time required for the restoration of the threshold from fatigue to normal, in denervated muscles, is approximately the same as that for the normal muscle.

Summary

(1) The average threshold for the *tibialis anticus* muscle when taken from the *peroneus communis* nerve was, for decerebrate animals 1.179, and for animals in urethane anaesthesia 3.08 β units; when taken from the normal muscle directly it was, for decerebrate animals 18.8, and for animals in urethane anaesthesia 29.84 β units.

(2) The average threshold for the denervated muscle was 61.28 β units.

(3) Fatigue increases the normal threshold stimulus, on the average, between 100 and 200 per cent, but may increase it more than 600 per cent. This increase is dependent upon the duration of the work, but varies with each animal. This variation may be due to the condition of the animal.

(4) Rest of 15 minutes to 2 hours restores the normal irritability of the nerve-muscle and muscle. This decrease of the threshold depends upon the time given to rest, the duration of the work, and also upon the condition of the animal.

(5) Fatigue and rest have the same effect on denervated muscle as on normal muscle.

It is with pleasure that I avail myself of this opportunity

of thanking Dr. E. G. Martin for the use of his apparatus for these experiments, and for suggestions and instruction given to me in the use of his method. I also wish to thank Dr. Walter B. Cannon for helpful supervision of my work.

TABLE I

The Effect of Fatigue on the Threshold Stimulus of the *Tibialis Anticus* in Decerebrate cats. Measurements taken by the Martin Method from (I) the *Peroneus Communis* nerve; and (II) the Muscle directly.

I			II		
Normal β	Maximum fatigue β	Increase in per cent	Normal β	Maximum fatigue β	Increase in per cent
1.25	5.63	350.4	20.69	74.5	260.5
2.75	14.02	409.8	25.4	43.0	69.5
2.96	7.03	137.5	13.8	82.5	498.0
0.62	2.64	325.9	25.7	65.9	156.5
0.481	1.82	278.3	21.2	168.0	693.0
0.39	1.42	264.1	11.75	12.89	9.5
0.753	0.925	22.8	17.23	43.04	150.0
0.597	1.436	140.5	33.07	130.0	293.5
0.319	0.823	157.9	24.9	120.0	382.0
0.674	1.341	98.9	9.99	41.3	313.5
2.5	7.4	196.0	14.7	99.1	574.0
0.687	0.88	28.0	6.75	20.3	201.0
1.465	1.761	20.2	32.1	70.17	118.5
1.15	3.02	162.6	10.98	35.5	224.0
1.85	2.4	29.7	13.88	37.0	166.5
0.432	0.935	116.4			
Average 1.179	3.34		18.8	69.54	

I. Percentage increase of average β = 183.5
II. Percentage increase of average β = 274

TABLE II

The Effect of Fatigue on the Threshold Stimulus of the *Tibialis Anticus* in cats in urethane anaesthesia. Measurements taken by the Martin Method from (I) the *Peroneus Communis* nerve; and (II) the Muscle directly.

I			II		
Normal β	Maximum fatigue β	Increase in per cent	Normal β	Maximum fatigue β	Increase in per cent
4.397	31.84	626.4	30.5	53.7	76.
7.05	23.7	236.3	54.9	112.9	105.5
5.45	21.5	294.5	49.3	195.	296.
1.98	2.91	46.9	22.3	51.75	132.
2.66	2.79	4.8	19.31	30.43	57.5
3.08	3.1	0.6	30.2	47.6	57.8
.644	1.64	154.6	32.7	71.3	118.
1.45	1.75	20.7	12.53	39.	201.5
1.15	1.61	40.	22.95	31.6	37.8
2.95	3.24	10.2	23.8	29.1	22.2
Average 3.081	9.408		29.849	66.238	

I. Percentage increase of average β = 208
II. Percentage increase of average β = 122

TABLE III

The Influence of Rest upon the Fatigue Threshold of the *Tibialis Anticus* in decerebrate cats. Measurements taken by the Martin Method from (I) the *Peroneus Communis* nerve; and (II) the Muscle directly.

	I			II		
Time of rest H. M.	Normal β	Fatigue β	β after rest	Normal β	Fatigue β	β after rest
.30	.62	1.45	1.285	25.7	43.7	18.48
1.00	.432	.935	*.578	17.23	43.04	21.3
1.30	.674	1.431	1.005	9.99	41.3	30.6
1.00	2.5	7.4	1.485	14.7	99.1	47.3
.30	1.85	2.4	1.85	10.98	35.5	15.9
1.00	3.08	3.1	†1.92	13.88	37.0	15.8
.15				24.9	120.0	81.3
.15				18.7	32.3	23.5
Average	1.526	2.771	1.353	17.01	56.649	31.77

* 45 min.
† 30 min.